Reviewers report

Title: Clinical prediction of 18F-FDG PET activity in sarcoidosis

Version: 2 Date: 3 June 2012

Reviewer: Francesco Bonella

Reviewers report:

General comments

The manuscript by Mostard et al reports on their experience with 18F-FDG PET in patients affected by sarcoidosis with persistent disabling symptoms. The authors found that applying a prediction model based on serum IL-2R and HRCT, it was possible to identify patients that need 18F-FDG PET to assess residual or occult inflammatory activity in sarcoidosis. The manuscript is well written and of certain interests, above all considering that the role of 18F-FDG PET is still under debate.

There are some concerns that need to be addressed.

Major concerns

C1 A recent study of Mostard et al (Ref 8 in the paper) demonstrated that the combination of sIL-2R and Neopterin yielded a sensitivity of 80 % and a specificity of 100% for detecting inflammatory activity as shown by PET. The reported PPV and NPV for the combined biomarkers (CMI) were 100% and 65% respectively. Neopterin or serum IL-2R alone showed both a weaker association. Why did the authors exclude Neopterin, or the combination of these 2 biomarkers from the prediction tool’s calculation? Moreover, did the authors perform ROC analysis with the combination of the two biomarkers (Neopterine and sIL-2R) and HRCT score to predict PET positivity? In my opinion it is an interesting point. If they performed that, which Se, Sp, PPV and NPV for PET positivity have been found?

C2 A recent study of Mostard et al (Ref 8 in the paper) showed that 75 % of the patients with persistent disease related symptoms had signs of inflammatory activity as detected by PET. Using the currently proposed internal predicting rule (calculated retrospectively) for PET positivity, PET would be needed in up to 46 % of these complicated patients, on the basis of the best possible cut-off. Considering that the 95 patients selected for this retrospective study belong to the original cohort of 122 patients (Ref 8), is this discrepancy in the percentage (75 % vs 46 %) due to the adjustment for overfitting by using the shrinkage factor? Does it means that about 30 % of the patients that have inflammatory activity (based on biomarkers but not on HRCT score) would not have additional benefit from receiving a PET? If my interpretation is correct, this percentage of patients has pulmonary inflammatory activity that can be assessed by HRCT. Can the authors elucidate this point?
C3 A comment concerns the title of the paper. I find that the title in the current form is quite ambiguous. The internally validated rule developed by the authors is based on biomarkers and HRCT and predicts PET positivity, and not PET activity.

I suggest to re-formulate the title as following: “A predictive tool for an effective use of 18F-FDG PET in assessing activity of sarcoidosis”.

C4 The authors define as “persistent disabling symptoms” the presence of more than one symptom that had substantial influence on quality of life, and that could not be explained from the results of routine investigations, including the absence of lung functional or chest radiographic deterioration. I cannot find either in the text or in the tables, a temporal indication on the persistency of these symptoms. Did the authors use a time range of 6 months or 2 years to define symptoms as persisting? Or can the authors indicate a mean observational time?

C5 Moreover I have some perplexities about the use of the term “unexplained” for the symptoms, as in materials and methods on page 5. The term “non organ specific symptoms” may fit better the definition given by the authors on page 4. I suggest to use the same term all over in the text.

Minor concerns

C6 On page 13, the authors write that “Among patients with a normal sIL-2R level, PET appeared …”. Can the authors report somewhere in the text or in the table 1 an upper limit of normal for sIL-2R in their lab? In the current manuscript and in the previous study of the same group (Ref 8) only the range of sIL-2R in 40 healthy controls has been reported (240-3154 IU/ml). However, Grutters et al (Chest, 2003) reported a value of 710 IU/ml as upper limit of normal. Do the authors intend, on page 13, patients with a sIL-2R level < 3154 IU/ml? If yes, please clarify this point in the methods.

C7 In the table 2 the comparison between the original model and the model after internal validation is shown. The p-value for the model after internal validation is not reported. Will the original p value also be influenced by the application of the shrinkage factor (0.93)? If this calculation is possible, please insert the p-value for the new regression.

C8 The title of the table 3 should be changed, for clarity reasons, as following: “Sensitivity, specificity, positive and negative predictive values for PET activity at consecutive cut-off points of the prediction rule score”.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests.